Remarks

The Office Action mailed December 6, 2000 has been received and reviewed. Claims 1-20 are pending in the application. All pending claims stand rejected. The application is to be amended as previously set forth. All amendments are made without prejudice or disclaimer. Reconsideration is respectfully requested.

1. Rejection of Claims 1-4, 7, 9-11, 18, 19, and 20 Under 35 U.S.C. § 103(a) As Unpatentable Over Koes et al., Souer et al., and Shalon et al.

Claims 1-4, 7, 9-11, 18, 19, and 20 stand rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Koes et al. ("Koes"), Souer et al.("Souer"), and Shalon et al. ("Shalon"). Applicants respectfully traverse the rejection, as hereinafter set forth.

M.P.E.P. 706.02(j) sets forth the standard for a Section 103(a) rejection:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). (Emphasis added).

Koes teaches a method of screening for *dTphI* insertions in a specific gene of a plant population using a PCR-based assay. In Koes, genomic DNA from a population of W138 was screened for transposable elements by using a gene-specific and a transposon-specific primer. Using the methods taught by Koes, a suitable template for hybridization is generated only when a transposon has been inserted into the gene.

Souer teaches a method of screening for new transposable mutations in genes of a mutated W138 plant. In Souer, total genomic DNA of mutated and wild-type plants was digested with a restriction enzyme and ligated to form monomeric circles. *dTph1* flanking sequences from mutant and wild-type plants were amplified by iPCR, and the amplification products taken from the mutant plant were cloned in an M13 vector to obtain a library of *dTph1* sequences. This library of *dTph1* sequences yielded probes which were subsequently differentially hybridized to iPCR amplification

products generated from mutant and wild-type plants.

Shalon teaches a DNA micro-array system for analyzing DNA samples using two-color fluorescent probe hybrization.

Applicants first respectfully submit the 35 U.S.C. § 103(a) obviousness rejections of claims 1-4, 7, 9-11, 18, 19, and 20 are improper because the combination of references fails to teach or suggest every limitation recited by the presently claimed invention.

Regarding presently amended independent claim 1, applicants submit the cited references fail to teach or suggest the element combination reciting:

> preparing an insertion element mutant library comprising a plurality of nucleic acid insertion elements and insertion element flanking sequences, said insertion element flanking sequences originating from a defined population of an organism wherein said gene insertion mutants are to be detected;
>
> amplifying said insertion element flanking sequences from said insertion element mutant library using at least one primer derived from a sequence of a nucleic acid insertion element of said plurality of nucleic acid insertion elements; and
>
> fixing a set of nucleic acid amplification products representing said insertion element flanking sequences derived from said insertion element mutant library to a solid support as target for hybridization.

The reference combination does not teach or suggest: 1) amplifying insertion element flanking sequences from an insertion element mutant library using a primer derived from a sequence of a nucleic acid insertion element; and 2) fixing the resulting nucleic acid amplification products to a solid support for amplification.

Applicants respectfully submit that Koes teaches away from the present invention by specifically requiring a gene-specific primer in the PCR amplification of flanking nucleic acid sequences. Applicants further submit that the deficiencies of Koes are not remedied by Souer or Shalon. Souer teaches iPCR using an insertion element specific primer. The methods of Souer, however, are drawn to amplification and screening of insertion flanking sequences of two individual plants (*i.e.*, a mutated plant and a wild-type plant). Thus, while Souer is narrowly drawn to screening for mutated genes in a specific mutant by comparing amplified flanking sequences of the mutant with amplified flanking sequences of a wild-type plant, the presently claimed invention is contrastingly drawn to amplification and screening of flanking sequences found in an insertion element mutant library for the purpose of identifying mutants for specific genes existing within in

a population.

Applicants therefore submit that the combination of Koes and Souer fails to teach or suggest the amplification of insertion element flanking sequences of an insertion element mutant library using a primer derived from a sequence of a nucleic acid insertion element.

Furthermore, since the combination of Koes and Souer does not teach or suggest amplifying flanking sequence portions of insertion elements from an insertion element mutant library using a primer derived from a nucleic acid insertion element, neither reference nor their combination could teach fixing the resulting nucleic acid amplification products to a solid support for amplification.

Applicants further submit that Shalon does not remedy the deficiencies of Koes since the Shalon's cited relevance is towards the use of micro-arrays, not towards the insertion element mutant library and amplification methods recited in the subject claim.

Thus, because the combined teachings of Koes, Souer and Shalon do not teach or suggest every limitation of independent claim 1, a *prima facie* case of obviousness has not been made out with respect to this claim. If an independent claim is nonobvious, then any claim depending from the independent claim is also nonobvious. M.P.E.P. §2143.03 (citing *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988)). Therefore, claims 2-4, 7, 9-11 and 20 are allowable as depending directly or indirectly from nonobvious independent claim 1.

Amended independent claims 18 and 19 contain limitations relating to the amplification of flanking sequences from a mutant library which are similar to those found in claim 1. Applicants respectfully submit that amended claims 18 and 19 are nonobvious over the cited references for the reasons discussed in relation to claim 1.

Moreover, it is respectfully submitted that one of ordinary skill in the art would not have been motivated to combine the teachings of Koes with the teachings of Souer in the manner suggested in the outstanding Office Action. The Office bears the burden of establishing a *prima facie* case of obviousness. This burden can only be satisfied:

> by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art *would lead* that individual to combine the relevant teachings of the references. *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). Indeed, the teachings of references can be combined only if there is some suggestion or incentive to do so. *ACS Hospital Systems, Inc. v. Montefiore Hospital*, 723 F.2d 1572,1577, 221 U.S.P.Q. 929, 933 (Fed. Cir. 1984).

Ex parte Obukowicz, 27 USPQ2d 1063 (B.P.A.I. 1993).

In this regard, applicants note that Koes specifically teaches a gene-specific primer in the PCR amplification of flanking nucleic acid sequences, while Souer contrastingly teaches iPCR using an insertion element specific primer. Applicants submit modifying the teachings of Koes to include the iPCR methods of Souer would impermissibly change one of the principles of operation of the Koes method. According to the M.P.E.P.:

> "If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims prima facie obvious." M.P.E.P. §2143.01 (citing *In re Ratti*, 123 USPQ 349 (CCPA 1959)).

Further in this regard, Koes teaches that the combination of a gene-specific primer and transposon-specific primer generates the relevant template which is exponentially amplified in PCR and used for hybridization detection. (Koes, page 8150, col. 1, second paragraph). Souer's iPCR method would thus be incompatible with the specific PCR and hybridization steps taught by Koes, and could not be incorporated therein. Accordingly, applicants submit that there is no desirability to combine these references since the proposed combination would destroy the Koes reference.

Additionally, the methods taught by Koes are described for use in detecting rare insertions of a transposable element into a specific gene within a population of plants (*Id.*), while the methods of Souer are described for use in detecting new unstable mutations in an individual plant line (W138) which already contains more than 200 copies of a transposable insertion mutant (Souer, page 677, Summary).

Applicants therefore respectfully submit that the methods taught by the subject references are inapposite to one another, and that one of ordinary skill in the art would not be motivated to make the proposed combination.

As such, applicants submit no suggestion or motivation exists, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine reference teachings, and there could be no reasonable expectation of success in such a combination, if such combination could be made. Applicants thus submit that the first and second elements of a *prima facie* case for obviousness have not been met with respect to the presently claimed invention.

Finally, based on the lack of motivation in the references and the art, it appears that the

combination of Koes and Souer could only have been based on hindsight provided by the disclosure of applicants' patent application. *See, e.g., In re Fritch,* 23 USPQ2d 1780 (Fed. Cir. 1992); *In re Fine,* 5 USPQ2d 1596, 1600 (Fed. Cir. 1988).

For the reasons stated above, applicants submit that claims 1-4, 7, 9-11, 18, 19, and 20 in condition for allowance. Applicants accordingly respectfully request that the 35 U.S.C. § 103 rejections be withdrawn, and the claims allowed.

2. Rejection of Claims 5, 6, 8 and 12 Under 35 U.S.C. § 103(a) As Being Unpatentable Over Koes, Souer, and Shalon as Applied to Claim 1, and Further in View of Vos

Claims 5, 6, 8 and 12 stand rejected under 35 U.S.C. § 103(a) as obvious over Koes, Souer, Shalon, and further in view of Vos et al. ("Vos"). Applicants respectfully traverse the rejection, as hereinafter set forth.

Vos teaches an AFLP technique of DNA fingerprinting. The AFLP technique taught by Vos is based on the selective PCR amplification of restriction fragments from a total digest of genomic DNA, and involves three steps: 1) restriction of the DNA and ligation of oligonucleotide adapters; 2) selective amplification of sets of restriction fragments; and 3) gel analysis of the amplified fragments. In Vos, the selective amplification is achieved by use of primers which extend into the restriction fragments using random bases, thus amplifying only those fragments in which the primer extensions match the nucleotides flanking the restriction sites. A second round of amplification uses primers based on the initial primers and extended by the addition of further random bases.

Applicants first respectfully submit that the rejected claims are allowable, for among other reasons, as depending from nonobvious independent 1 for the reasons previously discussed.

Applicants also respectfully submit that the reference combination does not teach or suggest all the claim limitations of claims 5, 6, 8, and 12, and thus does not meet the requirements of the third element of a *prima facie* case for obviousness. In this regard, applicants submit that the AFLP method taught by Vos differs from transposon display amplification in general as is recited in claim 5, and that the amplification step recited in claim 6 differs from the amplification method taught by Vos. Claims 8 and 12 depend from claims 6 and 5, respectively, and thus inherently incorporate the nonobvious limitations therein. (35 U.S.C. § 112, fourth paragraph).

More specifically, applicants submit that "transposon display amplification" as recited in

claims 5 and 6 requires knowledge of the sequence of the insertion element for sequence amplification, while the stated advantage of the AFLP technique taught by Vos is that DNA fragment patterns may be generated without such knowledge. (Vos, page 4407, Introduction). In this regard, "transposon display amplification" is described on pages 10 and 11 of the present *Specification* as using, in a pre-amplification reaction, "a primer based on the hexacutter site adapter and the insertion element is used in combination with a primer based on the tetracutter adapter site . . . ." (Emphasis added). (*Specification*, page 11, lines 4-5). Similarly, claim 6 contains a limitation reciting "amplifying insertion element flanking sequences using a primer based on a sequence of the biotinylated adaptor and on the insertion element sequence and a primer complementary to the second adaptor." (Emphasis added).

Applicants thus submit that Vos teaches away from the recited methods, since in the AFLP methods taught by Vos, ". . . sets of restriction fragments may be visualized without knowledge of [the] nucleotide sequence." (Vos, page 4407, Abstract).

As such, applicants respectfully request the obviousness rejection of claims 5, 6, 8 and 12 be withdrawn and the claims allowed.

3. Rejection of Claims 13-17 Under 35 U.S.C. § 103(a) As Unpatentable Over Koes et al., Souer et al., and Shalon et al.

Claims 13-17 stand rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Koes, Souer, and Shalon. Applicants respectfully traverse the rejection.

Applicants respectfully submit that claims 13-17 are allowable, for among other reasons, as depending, directly or indirectly, from nonobvious independent claim 1. Applicants respectfully refer the Office to the previous section discussing the rejection of claim 1, which is incorporated by reference herein with regard to the rejection of claims 13-17. It is therefore respectfully requested that the 35 U.S.C. § 103(a) rejections of claims 13-17 be withdrawn, and the claims be allowed.

Conclusion

In view of the amendments and remarks presented herein, applicants respectfully submit that claims 1-20 are allowable, and an early notice thereof is respectfully solicited. If questions should remain after consideration of the foregoing, the Examiner is kindly requested to contact applicants'

attorney at the address or telephone number given herein.

Respectfully submitted,

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Attachment: Marked up version of the amended claims

VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Twice amended) A method for simultaneous screening for one or more gene insertion mutants in a population of any organism comprising:

preparing an insertion element mutant library comprising a plurality of nucleic acid insertion elements and insertion element flanking sequences, said insertion element flanking sequences originating from a defined population of an organism wherein said gene insertion mutants are to be detected;

amplifying said insertion element flanking sequences from said insertion element mutant library using at least one primer derived from a sequence of a nucleic acid insertion element of said plurality of nucleic acid insertion elements; and

fixing a set of nucleic acid amplification products representing said insertion element flanking sequences derived from said insertion element mutant library to a solid support as target for hybridization.

2. (Twice amended) The method according to claim 1 wherein the set of nucleic acid amplification products representing said insertion element flanking sequences are obtained by iPCR using at least one primer or a set of primers based on a sequence of at least one nucleic acid insertion element.

4. (Twice amended) The method according to claim 3 further comprising reamplifying said at least one amplifyable genomic fragment using at least one primer based on a sequence of [an]a nucleic acid insertion element of said plurality of nucleic acid insertion elements.

16. (Amended) The kit according to claim 14 wherein the set of amplified insertion flanking sequences is present in a state selected from a group consisting of a soluble state and a dried state.

18. (Amended) A method for simultaneous screening for one or more gene insertion mutants in a cell line comprising:

preparing an insertion element mutant library comprising a plurality of nucleic acid insertion elements and insertion element flanking sequences, said insertion element flanking sequences originating from a cell line wherein said gene insertion mutants are to be detected;

amplifying said insertion element flanking sequences from said insertion element mutant library using at least one primer derived from a sequence of a nucleic acid insertion element of said plurality of nucleic acid insertion elements; and

fixing a set of nucleic acid amplification products representing said insertion element flanking sequences derived from said insertion element mutant library to a solid support as target for hybridization.

19. (Amended) A method for simultaneous screening for one or more gene insertion mutants in a population of any organism comprising:

preparing an insertion element mutant library comprising a plurality of nucleic acid insertion elements and insertion element flanking sequences, said insertion element flanking sequences originating from a defined population of an organism wherein said gene insertion mutants are to be detected;

amplifying said insertion element flanking sequences from said insertion element mutant library using at least one primer derived from a sequence of a nucleic acid insertion element of said plurality of nucleic acid insertion elements; and

producing a set of labelled amplification products representing said insertion element flanking sequences derived from said insertion element mutant library to use as probes to hybridize to a solid support to which one or more nucleic acids have been fixed as target(s) for hybridisation.

20. (Amended) The method according to claim 2 wherein said iPCR comprises:

digesting nucleic acid sequences of said insertion element mutant library with at least one restriction enzyme which optionally recognizes motifs of four nucleotides in genomic DNA, resulting in a collection of amplifyable genomic fragments;

ligating at least one amplifyable genomic fragment by self ligation; and

amplifying said at least one amplifyable genomic fragment using a [primers]primer based on a terminal part of an insertion element.